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Signed William Morell

Dated 22 March 2005

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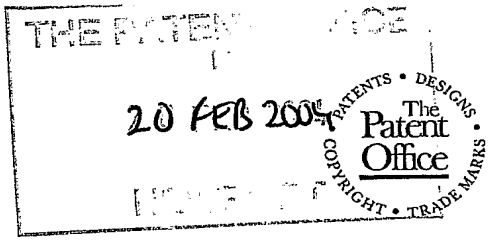


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Cardiff Road
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1. Your reference 101389-1

2. Patent application number
*(The Patent Office will fill in this part)* 20 FEB 2004 0403780.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 07822448003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)*

Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 08179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*
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| Priority documents | |
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| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
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| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 19.02.04

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer Bennett - 01625 230148

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# THERAPEUTIC AGENTS

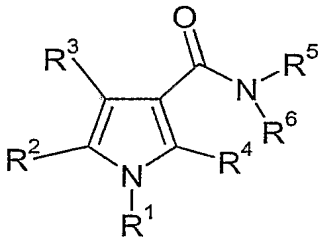
## Field of invention

The present invention relates to certain compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

## Background of the invention

It is known that certain $CB_1$ modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354).

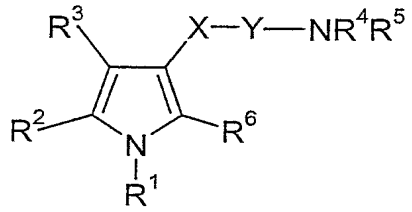
WO 03/027069 discloses pyrrole –3- carboxamides of formula A



A

in which $R^1$ and $R^2$ are each a phenyl group, optionally substituted with one or more halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy , trifluoromethyl, hydroxy, cyano or nitro; $R^3$ is hydrogen; $R^4$ is $CH_3$ ; $R^5$ is hydrogen or $(C_1\text{-}C_6)$alkyl; $R^6$ is cyclohexyl, $(C_1\text{-}C_6)$alkyl, cyclopentyl, cycloheptyl or cyclo$(C_3\text{-}C_7)$alkyl$(C_1\text{-}C_3)$alkyl, benzyl, phenyl, piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl each of which is optionally substituted or a group $NR^7R^8$ where $R^7$ is hydrogen or $(C_1\text{-}C_6)$alkyl; and $R^8$ is $(C_1\text{-}C_6)$alkyl or phenyl each of which is optionally substituted or $R^7$ and $R^8$ taken together with the nitrogen to which they are attached form a 5- to 10- membered saturated heterocyclic radical which is optionally substituted; or $R^5$ and $R^6$ taken together with the nitrogen to which they are attached form a 5- to 10- membered saturated heterocyclic radical which is optionally substituted wherein the optional substituents include $(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkoxy; are $CB_1$ modulators.

Co-pending application PCT/GB03/05569 discloses pyrrole –3- carboxamides of formula B



B

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

$R^1$ and $R^2$ independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

Z represents a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di $C_{1-3}$alkylamino, mono or di $C_{1-3}$alkylamido, $C_{1-3}$alkylsulphonyl, $C_{1-3}$alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di $C_{1-3}$alkyl carbamoyl, sulphamoyl and acetyl; and

$R^3$ is H, a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxymethyl group, trifluoromethyl, a hydroxy$C_{1-3}$alkyl group, an amino$C_{1-3}$alkyl group, $C_{1-3}$alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di $C_{1-3}$alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula –$CONHNR^aR^b$ wherein $R^a$ and $R^b$ are as defined for $R^4$ and $R^5$ respectively and;

X is CO or $SO_2$ ;

Y is absent or represents NH optionally substituted by a $C_{1-3}$alkyl group;

$R^4$ and $R^5$ independently represent :

a $C_{1-6}$alkyl group;

an (amino)$C_{1-4}$alkyl– group in which the amino is optionally substituted by one or more $C_{1-3}$alkyl groups;

an optionally substituted non-aromatic $C_{3-15}$carbocyclic group;

a ($C_{3-12}$cycloalkyl)$C_{1-3}$alkyl– group;

a group $-(CH_2)_r(\text{phenyl})_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more $C_{1-3}$alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

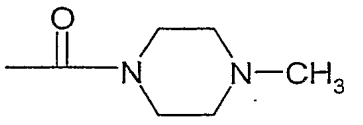
a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more $C_{1-3}$alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a $C_{1-5}$alkyl group, a $C_{1-5}$alkoxy group or halo;

or $R^4$ represents H and $R^5$ is as defined above;

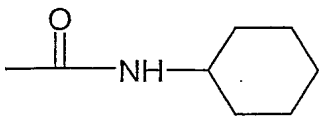
or $R^4$ and $R^5$ together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more $C_{1-3}$alkyl groups, hydroxy or benzyl ;

$R^6$ is H, a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxymethyl group, trifluoromethyl, a hydroxy$C_{1-3}$alkyl group, an amino$C_{1-3}$alkyl group, $C_{1-3}$alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di $C_{1-3}$alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein $R^a$ and $R^b$ are as defined for $R^4$ and $R^5$ respectively and;

with the proviso that when $R^6$ is methyl then the group $X\text{-}Y\text{-}NR^4R^5$ does not represent $CONHC_6H_{13}$ , $CONHC_{12}H_{25}$, $CONH_2$, $CONHCH_3$ , $CON(CH_3)_2$,



or

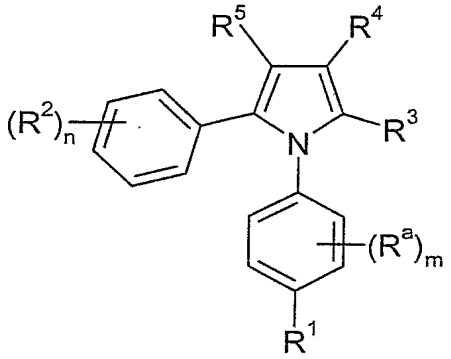


and with the further proviso that when $R^1$ and $R^2$ independently represent phenyl then Z is not an ortho methyl group as $CB_1$ modulators.

However, there is a need for $CB_1$ modulators with improved potency, selectivity, physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

Description of the invention

The invention relates to a compound of formula (I)



I

and pharmaceutically acceptable salts and solvates thereof, in which

$R^1$ represents a) a $C_{3-6}$alkoxy group substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^6S(O)_2O$ or $R^6S(O)_2NH$ in which $R^6$ represents a $C_{1-6}$alkyl group optionally substituted by one or more fluoro, or $R^6$ represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^7)_3$ Si in which $R^7$ represents a $C_{1-6}$alkyl group which may be the same or different;

$R^a$ represents halo, a $C_{1-3}$alkyl group or a $C_{1-3}$alkoxy group

m is 0, 1, 2 or 3;

$R^2$ represents a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, hydroxy, nitro, cyano or halo

n is 0, 1, 2 or 3;

$R^3$ represents H, a $C_{1-6}$alkyl group, a $C_{1-6}$alkoxy group or a $C_{1-6}$alkoxy$C_{1-6}$alkylene group which contains a maximum of 6 carbon atoms, each of which groups is optionally substituted by one or more fluoro or cyano;

$R^4$ represents

a) a group X-Y-$NR^8R^9$

in which X is CO or $SO_2$,
Y is absent or represents NH optionally substituted by a $C_{1-3}$alkyl group;

and $R^8$ and $R^9$ independently represent :
a $C_{1-6}$alkyl group optionally substituted by 1, 2, or 3 groups represented by W;
a $C_{3-15}$cycloalkyl group optionally substituted by 1, 2, or 3 groups represented by W;
an optionally substituted ($C_{3-15}$cycloalkyl)$C_{1-3}$alkylene group optionally substituted by 1, 2, or 3 groups represented by W;
a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;
a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more $C_{1-3}$alkyl groups, hydroxy or benzyl ;
a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more $C_{1-3}$alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a $C_{1-5}$alkyl group, a $C_{1-5}$alkoxy group or halo;
or $R^8$ represents H and $R^9$ is as defined above;
or $R^8$ and $R^9$ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more $C_{1-3}$alkyl groups, hydroxy, fluoro or benzyl;

or b) oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl or oxazolinyl, each optionally substituted by 1, 2 or 3 groups Z;

$R^5$ represents H or a $C_{1-3}$alkyl group;

Z represents a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di $C_{1-3}$alkylamino, $C_{1-3}$alkylsulphonyl, $C_{1-3}$alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di $C_{1-3}$alkyl carbamoyl and acetyl; and

W represents hydroxy, fluoro, a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, amino, mono or di $C_{1-3}$alkylamino, or a heterocyclic amine selected from morpholinyl, pyrrolidinyl, piperdinyl or piperazinyl in which the heterocyclic amine is optionally substituted by a $C_{1-3}$alkyl group or hydroxyl.

It will be understood that where a substituent Z is present in more than one group that these substituents are independently selected and may be the same or different. The same is true for W. Similarly when m 2 or 3 then the groups $R^a$ are independently selected so that they may be the same or different and similarly when n is 2 or 3 then the groups $R^2$ are independently selected so that they may be the same or different.

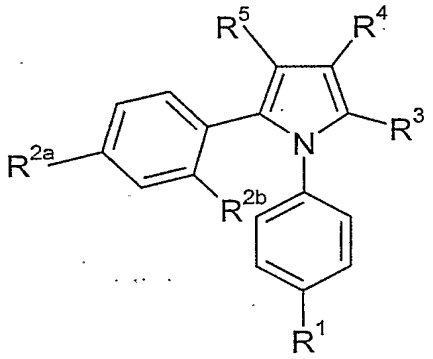
The term $C_{3-15}$cycloalkyl includes monocyclic, bicyclic, tricyclic and spiro systems for example, cyclopentyl, cyclohexyl and adamantyl.

The term heteroaryl means an aromatic 5- , 6-, or 7-membered monocyclic ring or a 9- or 10-membered bicyclic ring, with up to five ring heteroatoms selected from oxygen, nitrogen and sulfur. Suitable aromatic heteroaryl groups include, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl,

benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl. Preferably furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, oxazolyl thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl and more preferably pyrrolyl, thienyl, imidazolyl, oxazolyl or pyridyl.

Suitable saturated or partially unsaturated 5 to 8 membered heterocyclic groups containing one or more heteroatoms selected from nitrogen, oxygen or sulphur include, for example tetrahydrofuranyl, tetrahydropyranyl, 2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl, more preferably tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-4-yl or piperazin-1-yl.

A particular group of compounds of formula I is represented by formula IA



IA

in which $R^1$ is
a) a $C_{3-6}$alkoxy group substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^6S(O)_2O$ or $R^6S(O)_2NH$ in which $R^6$ represents a $C_{1-6}$alkyl group optionally substituted by one or more fluoro, or $R^6$ represents phenyl or a

heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^7)_3$ Si in which $R^7$ represents a $C_{1-6}$alkyl group which may be the same or different;

$R^{2a}$ represents chloro;

$R^{2b}$ represents chloro;

$R^3$ represents a $C_{1-3}$alkyl group;

$R^4$ represents a group $CONHNR^8R^9$ in which $NR^8R^9$ represents piperidino; and

$R^5$ represents H.

In one particular group of compounds of formula I or formula IA, $R^1$ represents a $C_{3-6}$alkoxy group substituted by one or more fluoro.

In another particular group of compounds of formula I or formula IA, $R^1$ represents a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z.

In a further particular group of compounds of formula I or formula IA, $R^1$ represents a group $R^6S(O)_2O$ or $R^6S(O)_2NH$ in which $R^6$ represents a $C_{1-6}$alkyl group optionally substituted by one or more fluoro, or $R^6$ represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z.

In a still further particular group of compounds of formula I or formula IA, $R^1$ represents a group of formula $(R^7)_3$ Si in which $R^7$ represents a $C_{1-6}$alkyl group which may be the same or different.

Further values of $R^1$ in compounds of formula I and formula IA now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Particularly $R^1$ is a group $R^6S(O)_2O$ in which $R^6$ represents a $C_{1-6}$alkyl group optionally substituted by one or more fluoro. More particularly $R^1$ is benzyloxy, trifluoromethylsulphonyloxy, 3,3,3-trifluoropropoxy, n-butylsulfonyloxy, n-propylsulfonyloxy or trimethylsilyl.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt,or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention. All tautomers, where possible, are included within the scope of the invention.

The present invention also encompasses prodrugs of a compound of formula I that is compounds which are converted into a compound of formula I in vivo.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

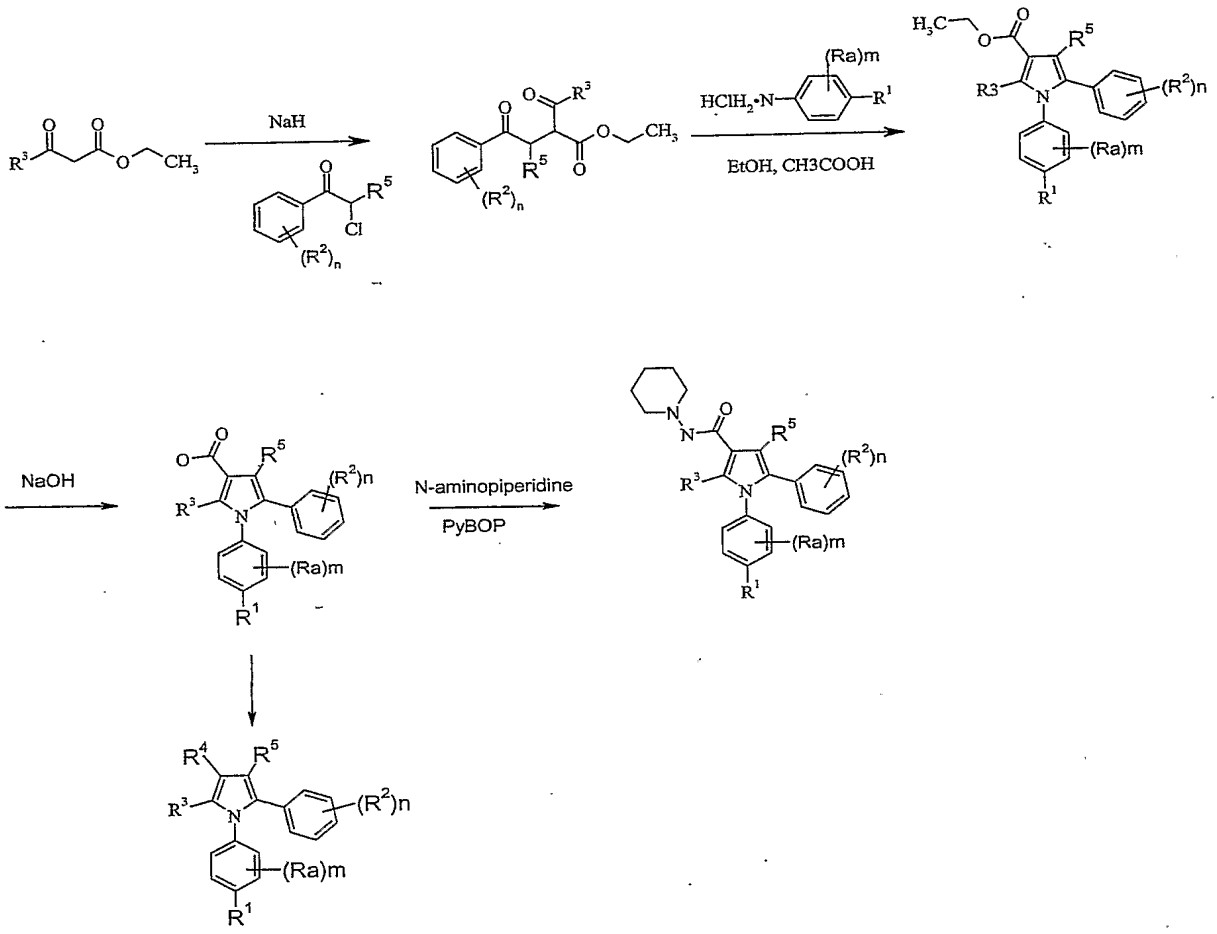
Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are one or more of the following:
1-[4(benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1H-pyrrole-3-carboxamide;
4-{5-(2,4-dichlorophenyl)-2-methyl-3-[piperidin-1-ylamino)carbonyl]-1*H*-pyrrol-1-yl}phenyl trifluoromethanesulfonate;
5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxamide ;
4-{5-(2,4-dichlorophenyl)-2-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrrol-1-yl}phenyl butane-1-sulfonate;
5-(2,4-Dichloro-phenyl)-2-methyl-1-(4-trimethylsilanyl-phenyl)-1H-pyrrole-3-carboxylic acid piperidin-1-ylamide; and
4-{5-(2,4-dichlorophenyl)-2-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrrol-1-yl}phenyl propane-1-sulfonate
as well as pharmaceutically acceptable salts thereof.

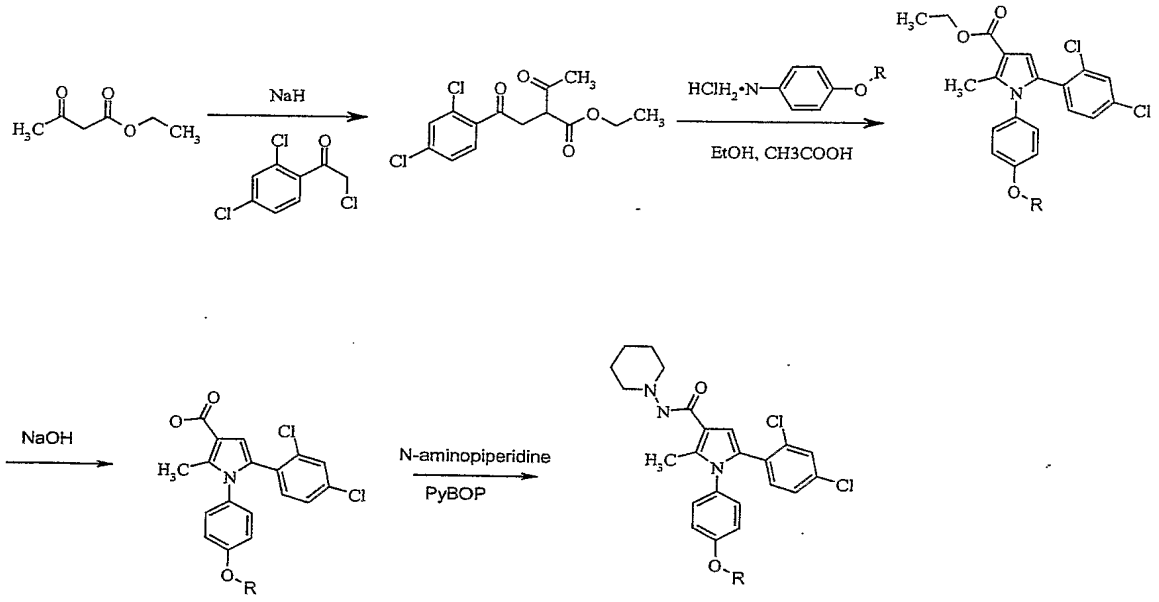
Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

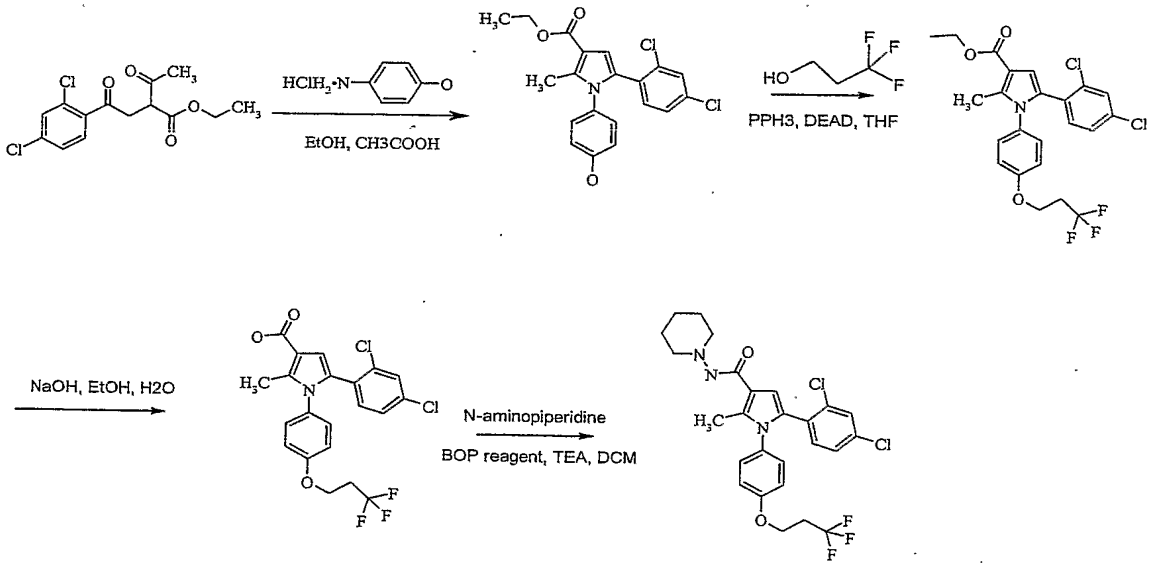
General Route



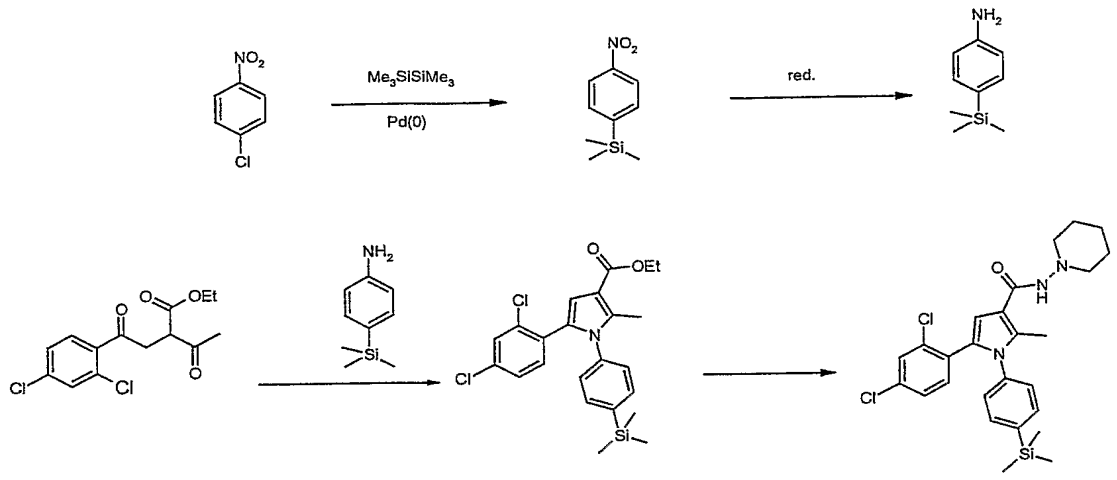
## Synthetic Route 1




## Synthetic Route 2



**Synthetic Route 3**




Certain intermediate compounds are believed to be novel and form part of the present invention.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in

the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-

compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and atherosclerosis. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety,

or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present

invention also includes a compound of the present invention in combination with a bile acid binding resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-coagulant;

an omega-3 fatty acid ;

another anti-obesity compound;

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a

salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

10µg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200µl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100µM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1µCi [$^{35}$S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [$^{35}$S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.
The compounds of the invention are selective CB1 antagonists or inverse agonists. The potency, selectivity profile and side effect propensity may limit the clinical usefulness of hitherto known compounds with alleged CB1 antagonistic/inverse agonistic properties. In this regard, preclinical evaluation of compounds of the present invention in models of gastrointestinal and/or cardiovascular function indicates that they offer significant advantages compared to representative reference CB1 antagonist/inverse agonist agents.

The compounds of the present invention may provide additional benefits in terms of improved potency, improved selectivity, improved bioavailability, better half-life in plasma, better blood brain barrier permeability, improved plasma protein binding or better solubility compared to representative reference CB1 antagonist/inverse agonist agents.

Examples

Abbreviations

DCM - dichloromethane
DMF - dimethylformamide
DMAP - 4-dimethylaminopyridine
EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
TEA – triethylamine
TFA – trifluoroacetic acid
DMSO-dimethyl sulfoxide
DEA - Diethylamine
PCC - Pyridinium chlorochromate
PyBOP - benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate
HBTU - *O*-Benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium Hexafluorophosphate
DAST-(diethyl amino)sulphur trifluoride
DIEA - *N,N*-diisopropylethylamine
t triplet
s singlet

| | |
|---|---|
| d | doublet |
| q | quartet |
| qvint | quintet |
| m | multiplet |
| br | broad |
| bs | broad singlet |
| dm | doublet of multiplet |
| bt | broad triplet |
| dd | doublet of doublet |

General Experimental Procedures

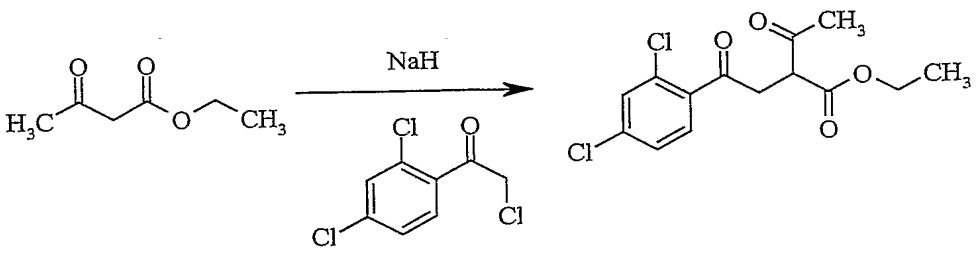
Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). $^1$H NMR measurements were performed on either a Varian Mercury 300 or a Varian Inova 500, operating at $^1$H frequencies of 300 and 500 MHz respectively. Chemical shifts are given in ppm with $CDCl_3$ as internal standard. $CDCl_3$ is used as the solvent for NMR unless otherwise stated. Purification was performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M $NH_4Ac$:acetonitrile 95:5).

For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

**Examples of the Invention**

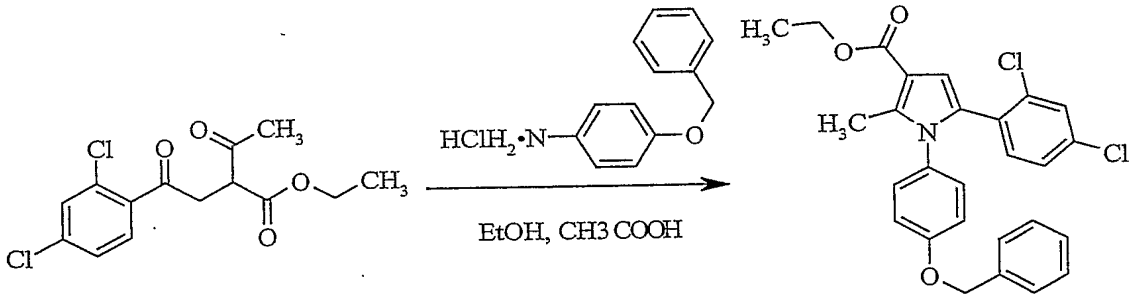
**Example 1**

**Step A** Ethyl 2-Acetyl-4-(2,4-dichlorophenyl)-4-oxobutanoate




Ethylacetoacetate (6.0 mL, 47.4 mmol) was added to a suspension of sodium hydride (3.0 g, 60% by weight, 75 mmol) in THF (250 mL) under $N_2$ and after 15 minutes, 2, 2', 4'-trichloroacetophenone (15.0 g, 67.1 mmol) was added. After stirring at room temperature for 18h, the reaction was quenched by adding saturated aq $NH_4Cl$ and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (10:1 hexanes/EtOAc) to afford Ethyl 2-Acetyl-4-(2,4-dichlorophenyl)-4-oxobutanoate as an oil (5.6 g, 37%): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $J$ = 8.3 Hz, 1H), 7.50 (d, $J$ = 1.9 Hz, 1H), 7.30 (dd, $J$ = 8.4, 2.0 Hz, 1H), 4.00–4.20 (m, 3H), 3.20–3.50 (m, 2H), 2.20 (s, 3H), 1.10-1.30 (m, 3H); ESI MS *m/z* 317 [$C_{14}H_{14}Cl_2O_4$ + H]$^+$.

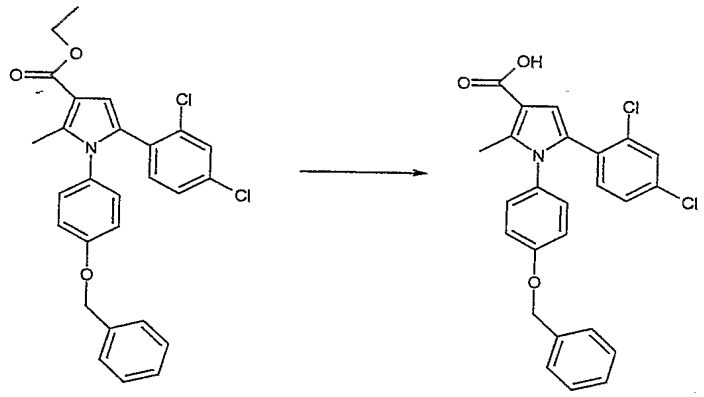
**Step B** Ethyl 1-[4-benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate




A solution of Ethyl 2-Acetyl-4-(2,4-dichlorophenyl)-4-oxobutanoate from **Ex1, Step A** (2.85 g, 9.0 mmol) and 4-benzyloxyaniline hydrochloride (2.14 g, 9.1 mmol) in 1:1 ethanol/acetic acid (80 mL) was heated at reflux for 18h. After cooling, the solution was partially concentrated and diluted with ethyl acetate. It was washed with saturated $NaHCO_3$ solution, and the organic layer was dried ($MgSO_4$) and concentrated. The residue

was purified by flash column chromatography (10:1 hexanes/EtOAc) to afford the title compound as a white solid (1.67 g, 39%): $^1$H NMR (300 MHz, $CDCl_3$) δ 6.90–7.40 (m, 12H), 6.73 (s, 1H), 5.02 (s, 2H), 4.31 (q, $J$ = 7.1 Hz, 2H), 2.40 (s, 3H), 1.36 (t, $J$ = 7.1 Hz); ESI MS *m/z* 480 $[C_{27}H_{23}Cl_2NO_3 + H]^+$; HPLC (Method A) 99.6% (AUC), $t_R$ = 36.2 min.

**Step C** 1-[4-benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid



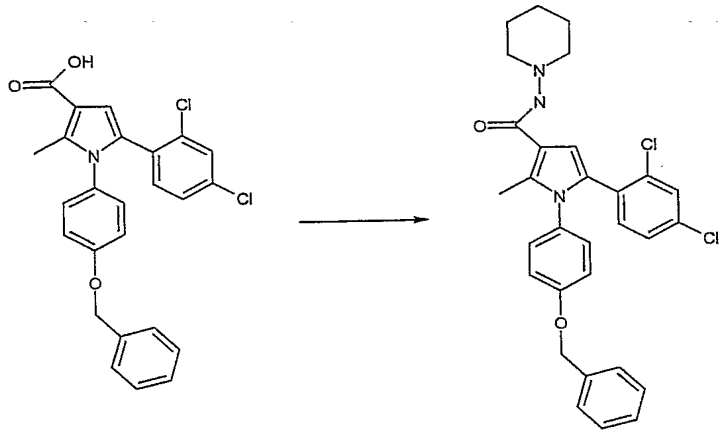
Ethyl 1-[4-benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate from **EX1, Step B** (400 mg, 0.833 mmol) and sodium hydroxide (1.417 g, 35.42 mmol) were refluxed in ethanol (20 ml) 1.5 hour. The solvent was evaporated and the mixture redissolved in water and neutralised with HCl (4M). The product was collected by filtration, washed with water (500 ml) and air dried over night. The crude product (375 mg, 99%) was used in steps described below without further purification.

$^1$H NMR (399.964 MHz) δ 7.45-7.10 (m, 6H), 7.10-6.75 (m, 7H), 5.00 (s, 2H), 4.00-3.00 (br, 1H), 2.37 (s, 3H).

$^{13}$C NMR (100.580 MHz) δ 172.87, 158.05, 136.84, 136.66, 135.31, 133.89, 133.49, 131.21, 130.95, 129.51, 129.23, 128.76, 128.45, 128.28, 127.86, 126.48, 116.77, 114.84, 112.91, 70.32, 12.74.

MS *m/z* 452, 454, 456 $(M+H)^+$.

**Step D** 1-[4(benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1H-pyrrole-3-carboxamide



1-[4-benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from **Ex1,Step C** (174 mg, 0.385 mmol) was dissolved in DCM (1 ml) and TEA (0.5 ml) under $N_2$ (g) and cooled to –78°C. Benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate dissolved in DCM (0.5 ml) was added dropwise followed immedately by the addition of 1-aminopiperidine (45 mg, 0.454 mmol). The reaction was continued at –78°C under $N_2$ (g) for 1 hour and then at room temperture over night. The mixture was extracted with water and dried over $MgSO_4$. Finally the product was purified by flash chromatography ($SiO_2$, toluene:ethylacetate 9:1) to give a slightly yellow powder (98 mg, 48%).

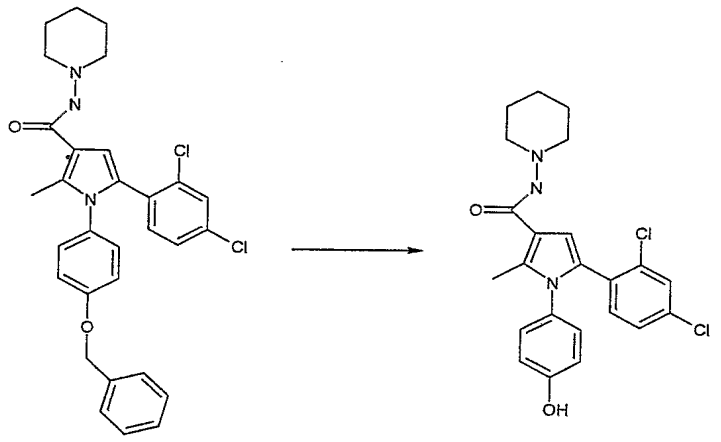
$^1$H NMR (399.964 MHz) δ 7.45-7.10 (m, 6H), 7.10-6.80 (m, 6H), 6.65-6.55 (br, 1H), 6.45-6.35 (br, 1H), 5.00 (s, 2H), 3.00-2.80 (br, 4H), 2.40 (s, 3H), 1.80-1.65 (br, 4H), 1.50-1.35 (br, 2H).

$^{13}$C NMR (100.580 MHz) δ 163.69, 158.49, 136.59, 136.19, 135.45, 134.32, 133.75, 130.69, 130.45, 129.57, 129.42, 128.83, 128.44, 128.39, 127.80, 126.73, 115.20, 114.25, 108.37, 70.47, 57.48, 25.76, 23.58, 12.61.

MS *m/z* 534, 536, 538 $(M+H)^+$.

## Example 2

**Step A** 5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide



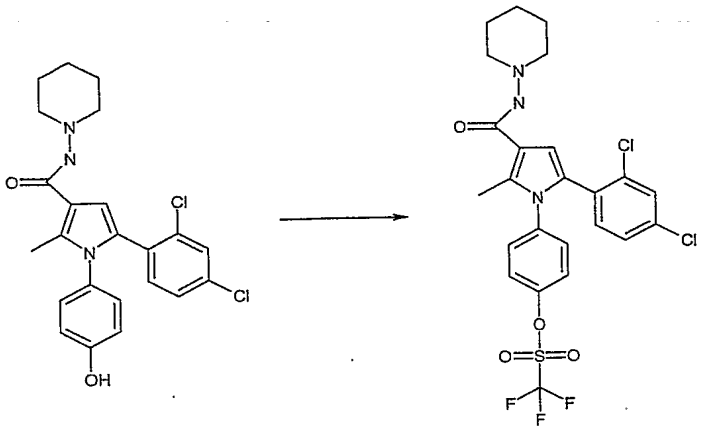
1-[4(benzyloxy)phenyl]-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1H-pyrrole-3-carboxamide from **Example 1, Step D** (98 mg, 0.183 mmol) and dimethyl sulfide (70 mg, 1.126 mmol) were dissolved in DCM (3 ml). Boron trifluoride etherate (224 mg, 1.578 mmol) was added dropwise and the reaction continued at room temperature 24 hours. The mixture was extracted with water and dried over $MgSO_4$. The crude product (77 mg, 95%) was used in steps described below without further purification.

$^1$H NMR (399.964 MHz) δ 7.32-7.24 (m, 1H), 7.10-6.95 (m, 2H), 6.95-6.85 (m, 2H), 6.80-6.75 (m, 2H), 6.68 (s, 1H), 6.43 (s, 1H), 3.35-3.25 and 3.07-2.97 (two multiplets, 3H), 2.90-2.77 (br, 1H), 2.40 (s, 3H), 2.10-1.82 and 1.75-1.50 (two multiplets, 6H), 1.40-1.30 (m, 1H).

$^{13}$C NMR (100.580 MHz) δ 167.07, 156.10, 136.07, 135.59, 134.40, 133.77, 130.62, 130.22, 129.88, 129.48, 126.67, 115.99, 110.69, 108.48, 57.40, 25.34, 22.50, 12.74.

MS *m/z* 444, 446, 448 $(M+H)^+$.

**Step B** 4-{5-(2,4-dichlorophenyl)-2-methyl-3-[piperidin-1-ylamino)carbonyl]-1*H*-pyrrol-1-yl}phenyl trifluoromethanesulfonate



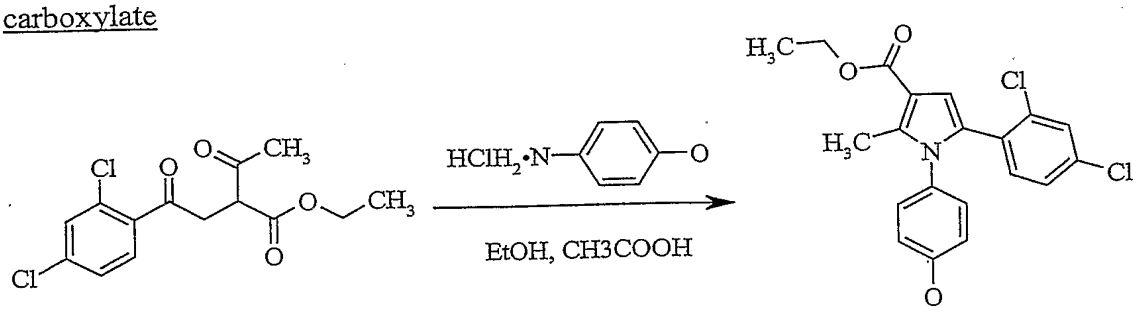
5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide , **Ex2, Step A** (44 mg, 0.099 mmol) was dissolved in DCM (3 ml) and TEA (40 µl) and cooled to -78°C. Trifluoromethane sulfuric anhydride (350 µl, 0.208 mmol) was added and the reaction continued at -78°C for 1 hour. The mixture was extracted with cold $NaHCO_3$ (aq) and water and dried over $MgSO_4$. The product was purified by flash chromatography ($SiO_2$, toluene:ethylacetate 9:1) and preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at about 80% acetonitrile) to give the subtitle compound as a slightly yellow powder (3 mg, 6%).

$^1$H NMR (399.964 MHz) δ 7.35-6.95 (m, 7H), 6.70-6.40 (br, 1H), 6.41 (s, 1H), 2.88 (s, 4H), 2.43 (s, 3H), 1.85-1.70 (s, 4H), 1.50-1.40 (s, 2H).

MS *m/z* 576, 578, 580 $(M+H)^+$.

**Example 3**

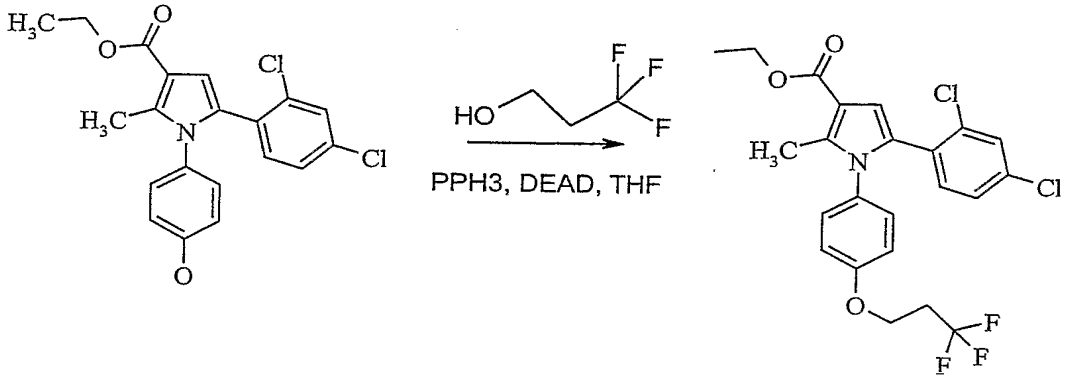
**Step A**. Ethyl 5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate




A solution of Ethyl 2-Acetyl-4-(2,4-dichlorophenyl)-4-oxobutanoate, from **Ex1, Step A** (5.45 g, 17.18 mmol), 4-aminophenol (2.40 g, 21.99 mmol), and acetic acid (10 mL) in

ethanol (15 mL) was heated at reflux for 14 hours. After cooling, the reaction was quenched by adding saturated $NaHCO_3$ solution and extracted into EtOAc. The organic layer was dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 9:1 hexanes/EtOAc) to afford Ethyl 5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyll-1*H*-pyrrole-3-carboxylate (2.87 g, 43%) as an oil. A portion of this material was recrystallized from hexanes/ethyl acetate to afford Ethyl 5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyll-1*H*-pyrrole-3-carboxylate as a white solid.: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.25–7.30 (m, 1H), 7.00–7.05 (m, 2H), 6.80–6.95 (m, 2H), 6.70–6.75 (m, 3H), 6.30–6.40 (broad s, 1H), 4.32 (q, $J$ = 6.9 Hz, 2H), 2.38 (s, 3H), 1.36 (t, $J$ = 7.2 Hz, 3H); ESI MS *m/z* 394 $[C_{20}H_{17}Cl_2NO_3 + H]^+$.

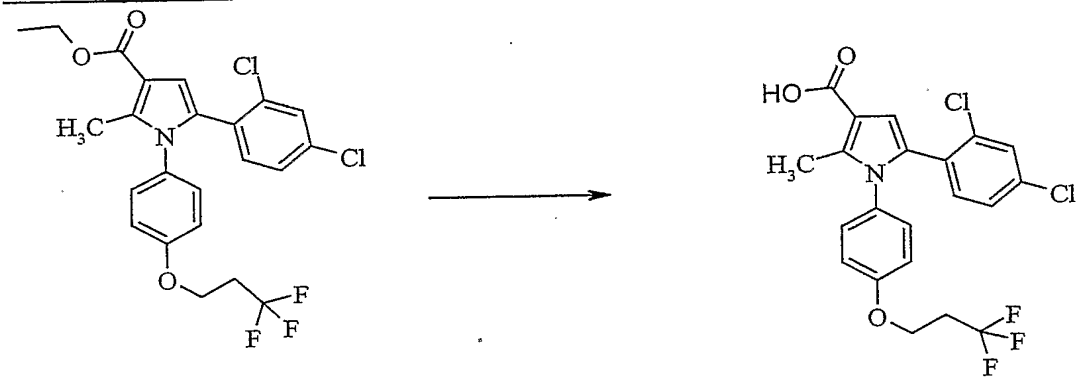
**Step B**. Ethyl 5-(2,4-dichlorophenyl)-2-methyl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxylate




A solution of Ethyl 5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyll-1*H*-pyrrole-3-carboxylate, from **Ex3, Step A** (2.87 g, 7.35 mmol) in THF (30 mL) was treated with 3,3,3-trifluoropropan-1-ol (0.65 mL, 7.37 mmol), triphenylphosphine (1.94 g, 7.40 mmol) and diethylazodicarboxylate (1.20 mL, 7.72 mmol) at 0 °C. The resulting solution was stirred at room temperature for 14 hours. The solution was concentrated under reduced pressure and the residue was taken in ethyl acetate. This solution was washed with water and the organic layer was dried ($MgSO_4$), and concentrated to afford the crude product. The crude product was purified by flash column chromatography (silica gel, 8:1 hexanes/EtOAc) to afford Ethyl 5-(2,4-dichlorophenyl)-2-methyl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxylate (0.90 g, 25%): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, $J$ = 1.9 Hz, 1H), 7.00–7.10 (m, 4H), 6.80 (d, $J$ = 8.9 Hz, 2H), 6.71 (d, $J$ =

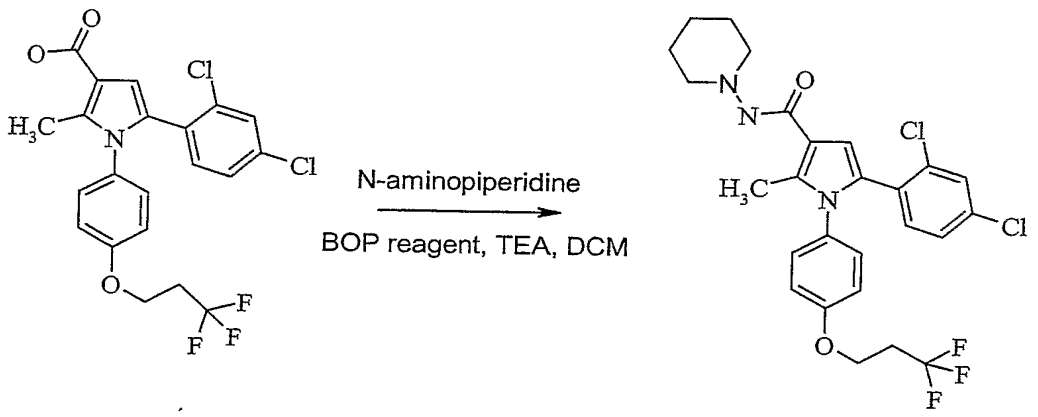
1.5 Hz, 1H), 4.30 (q, $J$ = 7.1 Hz, 2H), 4.10–4.20 (m, 2H), 2.55–2.65 (m, 2H), 2.38 (s, 3H), 1.36 (t, $J$ = 7.1 Hz, 3H); ESI MS *m/z* 486 $[C_{24}H_{22}Cl_2F_3NO_2 + H]^+$.

**Step C.** 5-(2,4-dichlorophenyl)-2-methyl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxylic acid



A solution of Ethyl 5-(2,4-dichlorophenyl)-2-methyl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxylate, from **Ex3, StepB** (0.96 g, 1.97 mmol) in ethanol (20 mL) was combined with a 1.0 M solution of NaOH (10 mL, 10.0 mmol). The resulting solution was heated at reflux for 16 hours. It was then poured into ice-cold 1 N HCl solution and extracted into EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to afford 5-(2,4-dichlorophenyl)-2-methyl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxylic acid (0.75 g, 83%) as a yellow powder: $^1$H NMR (300 MHz, $CD_3OD$) δ 7.36 (s, 1H), 7.15–7.17 (m, 3H), 7.05–7.10 (m, 2H), 6.90–7.00 (m, 3H), 6.71 (d, $J$ = 8.7 Hz, 1H), 6.62 (d, $J$ = 3.9 Hz, 1H), 4.19 (t, $J$ = 6.0 Hz, 2H), 2.65–2.70 (m, 2H), 2.35 (s, 3H), 1.90–1.95 (m, 2H); ESI MS *m/z* 458 $[C_{25}H_{26}ClN_3O_4 + H]^+$.

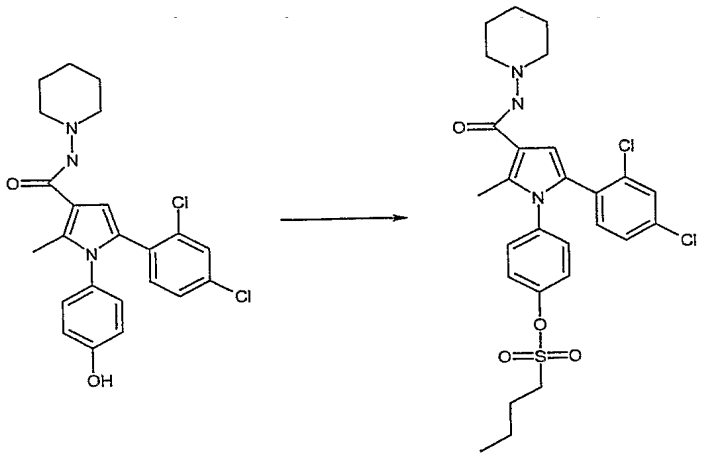
**Step D.** 5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxamide




A solution of 5-(2,4-dichlorophenyl)-2-methyl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxylic acid,from **Ex3, StepC** (0.64 g, 1.40 mmol) in $CH_2Cl_2$ (5 mL) under $N_2$ was treated with 1–aminopiperidine (0.19 mL, 1.76 mmol), BOP reagent (1.04 g, 2.35 mmol) and triethylamine (0.65 mL, 4.66 mmol). The solution was stirred at room temperature for 2 days. It was washed with water and the organic layer was dried ($MgSO_4$), and concentrated to afford the crude product. The crude product was purified by flash column chromatography (silica gel, 2:3 hexanes/EtOAc) to afford 5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1-(4-(3,3,3-trifluoropropoxyphenyl))-1*H*-pyrrole-3-carboxamide (0.22 g, 30%) as a white powder: M.P. 237–239 °C: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.18 (d, $J$ = 0.5 Hz, 1H), 7.07 (d, $J$ = 6.7 Hz, 2H), 7.05 (d, $J$ = 3.2 Hz, 2H), 6.60 (s, 1H), 4.19 (t, J = 6.2 Hz, 2H), 2.80–2.85 (m, 4H), 2.60–2.70 (m, 2H), 2.33 (s, 3H), 1.70–1.75 (m, 4H), 1.40–1.45 (m, 2H); ESI MS *m/z* 540 $[C_{26}H_{26}Cl_2F_3N_3O_2 + H]^+$; HPLC (Method A) 89.3% (AUC), $t_R$ = 17.8 minutes.

**Example 4**

4-{5-(2,4-dichlorophenyl)-2-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrrol-1-yl}phenyl butane-1-sulfonate



5-(2,4-dichlorophenyl)-1-(4-hydroxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide, from **Ex2, Step A** (66 mg, 0.147 mmol) from (b) and DMAP (27 mg, 0.221 mmol) were dissolved in dry DCM (2 ml) under $N_2$ (g). TEA (100 µl, 0.717 mmol) and 1-Butansulfonyl chloride (40 µl, 0.311 mmol) were added and the reaction continued at room temperature for 6 hours under $N_2$ (g). The mixture was extracted with water and dried over $MgSO_4$. The product was purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at about 100% acetonitrile) to give the subtitle compound as a white powder (42 mg, 50%).

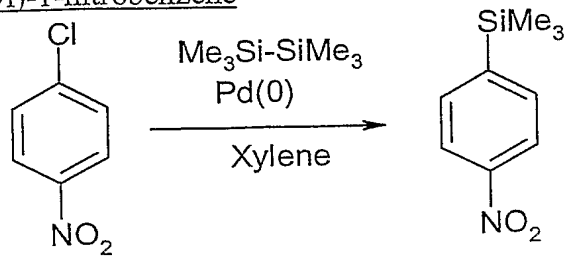
$^1$H NMR (399.964 MHz) δ 7.35-6.95 (m, 7H), 6.70-6.40 (br, 1H), 6.40 (s, 1H), 3.24 (t, 2H), 2.98-2.78 (br, 4H), 2.42 (s, 3H), 2.02-1.88 (m, 2H), 1.82-1.68 (br, 4H), 1.57-1.43 (m, 2H), 1.50-1.38 (br, 2H), 0.97 (t, 3H).

$^{13}$C NMR (100.580 MHz) δ 163.41, 148.48, 136.19, 135.85, 135.45, 134.81, 133.69, 130.23, 129.84, 129.70, 129.16, 126.93, 122.68, 114.94, 108.96, 57.48, 50.88, 25.75, 25.63, 23.57, 21.59, 13.64, 12.65.

MS *m/z* 564, 566, 568 $(M+H)^+$.

**Example 5**

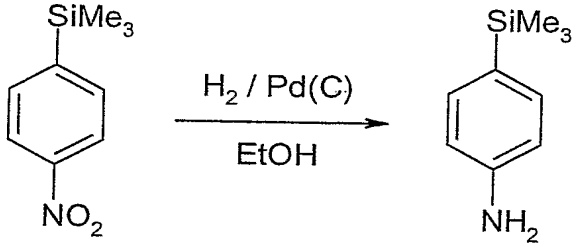
**Step A.** 4-(Trimethylsilyl)-1-nitrobenzene



1-Chloro-4-nitrobenzene (2.25 g, 14.3 mmol), hexamethyldisilane (8.98 g, 61.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (450 mg, 0.39 mmol) in xylene (7 ml) was sealed under nitrogen and stirred at 160°C for 4 hours. The mixture was cooled , 100 ml hexane was added, and the mixture filtered through a pad of Celite. Evaporation of the filtrate gave a dark oil. Flash-chromatography (silica, hexane:$CH_2Cl_2$ 95:5, 90:10) afforded 1.63 g (68%) of the title compound.

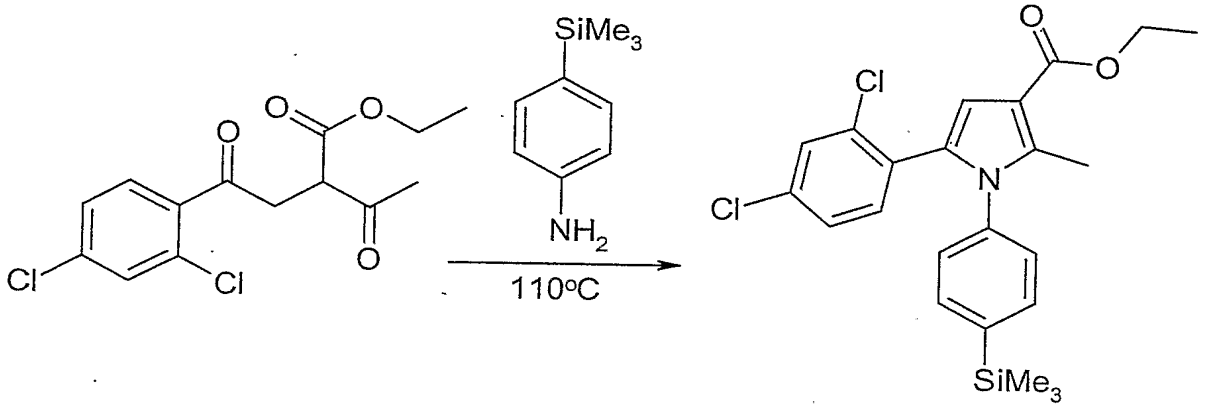
$^1$H NMR ($CDCl_3$): δ 8.19 (2H, d), 7.69 (2H, d), 0.34 (9H, s)

**Step B.** 4-(Trimethylsilyl)aniline




4-(Trimethylsilyl)-1-nitrobenzene, **Ex5, Step A** (1.63 g, 8.35 mmol) dissolved in ethanol (50 ml) was added 5% palladium on charcoal (500 mg, 0.23 mmol), and stirred under 1 atm of hydrogen pressure overnight. The mixture was then filtered through a pad of Celite and concentrated under reduced pressure, giving 1.3 g (94%) of the title compound.

**Step C.** 5-(2,4-Dichloro-phenyl)-2-methyl-1-(4-trimethylsilanyl-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester



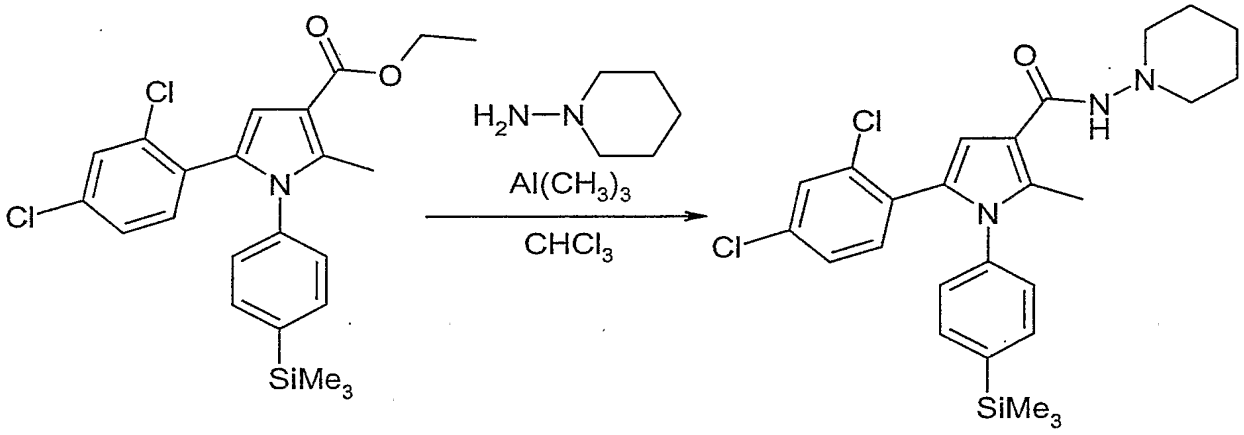

2-[2-(2,4-Dichloro-phenyl)-2-oxo-ethyl]-3-oxo-butyric acid ethyl ester, from **Ex1, Step A** (1.36 g, 4.3 mmol) and 4-(Trimethylsilyl)aniline (0.71 g, 4.3 mmol) was stirred at 110 °C

for 72 hours. Flash-chromatography (silica, hexane:EtOAc 95:5, 90:10) afforded 217 mg (12%) of the title compound.

$^1$H NMR ($CDCl_3$): δ 7.46 (2H, d), 7.31 (2H, m), 7.12-7.04 (4H, m), 4.34 (2H, q), 2.43 (3H, s), 1.39 (3H, t), 0.28 (9H, s)

MS m/z 469 (M+Na)

**Step D.** 5-(2,4-Dichloro-phenyl)-2-methyl-1-(4-trimethylsilanyl-phenyl)-1H-pyrrole-3-carboxylic acid piperidin-1-ylamide




To a solution of aminopiperidine (133 µl, 1.23 mmol) in dry chloroform (2 ml), was added dropwise under nitrogen a solution of trimethylaluminum in toluene (613 µl, 2 M sol., 1.23 mmol). The mixture was kept at r.t. with stirring for an additional 1 h. 5-(2,4-Dichloro-phenyl)-2-methyl-1-(4-trimethylsilanyl-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester (217 mg, 0.49 mmol) dissolved in dry chloroform (1 ml) was then added and the solution was warmed to 45 °C and stirred for 19 hours under nitrogen. The reaction mixture was poured carefully into 10 ml of 2 M HCl and the resultant mixture was stirred at 40 °C for 30 min. The layers were separated and the aqueous layer was extracted with chloroform (2x15 ml). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated under reduced pressure. Flash-chromatography (silica, hexane:EtOAc 80:20) afforded 36 mg (16%) of the title compound as a white solid.

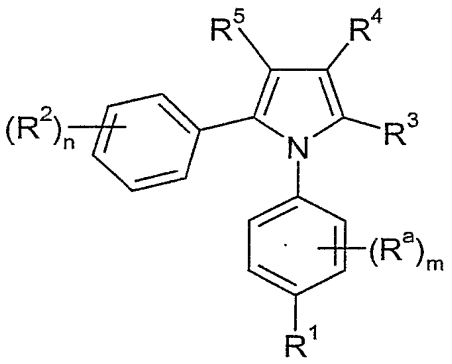
$^1$H NMR ($CDCl_3$): δ 7.47 (2H, d), 7.33 (2H, d), 7.08-7.00 (4H, m), 2.92 (4H, m), 2.45 (3H, s), 1.77 (4H, m), 1.48 (2H, m), 0.29 (9H, s)

MS m/z 523 (M+Na)

HPLC: 92.4%.

Claims

1. A compound of formula (I)



I

and pharmaceutically acceptable salts and solvates thereof, in which

$R^1$ represents a) a $C_{3-6}$alkoxy group substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^6S(O)_2O$ or $R^6S(O)_2NH$ in which $R^6$ represents a $C_{1-6}$alkyl group optionally substituted by one or more fluoro, or $R^6$ represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^7)_3$ Si in which $R^7$ represents a $C_{1-6}$alkyl group which may be the same or different;

$R^a$ represents halo, a $C_{1-3}$alkyl group or a $C_{1-3}$alkoxy group

m is 0, 1, 2 or 3;

$R^2$ represents a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, hydroxy, nitro, cyano or halo

n is 0, 1, 2 or 3;

$R^3$ represents H, a $C_{1-6}$alkyl group, a $C_{1-6}$alkoxy group or a $C_{1-6}$alkoxy$C_{1-6}$alkylene group which contains a maximum of 6 carbon atoms, each of which groups is optionally substituted by one or more fluoro or cyano;

$R^4$ represents

a) a group X-Y-$NR^8R^9$

in which X is CO or $SO_2$,

Y is absent or represents NH optionally substituted by a $C_{1-3}$alkyl group;

and $R^8$ and $R^9$ independently represent :

a $C_{1-6}$alkyl group optionally substituted by 1, 2, or 3 groups represented by W;

a $C_{3-15}$cycloalkyl group optionally substituted by 1, 2, or 3 groups represented by W;

an optionally substituted ($C_{3-15}$cycloalkyl)$C_{1-3}$alkylene group optionally substituted by 1, 2, or 3 groups represented by W;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more $C_{1-3}$alkyl groups, hydroxy or benzyl ;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more $C_{1-3}$alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a $C_{1-5}$alkyl group, a $C_{1-5}$alkoxy group or halo;

or $R^8$ represents H and $R^9$ is as defined above;

or $R^8$ and $R^9$ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more $C_{1-3}$alkyl groups, hydroxy, fluoro or benzyl;

or b) oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl or oxazolinyl,

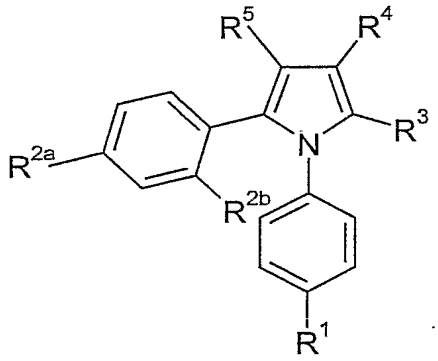
each optionally substituted by 1, 2 or 3 groups Z;

$R^5$ represents H or a $C_{1-3}$alkyl group;

Z represents a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di $C_{1-3}$alkylamino, $C_{1-3}$alkylsulphonyl, $C_{1-3}$alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di $C_{1-3}$alkyl carbamoyl and acetyl; and

W represents hydroxy, fluoro, a $C_{1-3}$alkyl group, a $C_{1-3}$alkoxy group, amino, mono or di $C_{1-3}$alkylamino, or a heterocyclic amine selected from morpholinyl, pyrrolidinyl, piperdinyl or piperazinyl in which the heterocyclic amine is optionally substituted by a $C_{1-3}$alkyl group or hydroxyl.

2. A compound of formula (IA)




IA

in which $R^1$ is
a) a $C_{3-6}$alkoxy group substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^6S(O)_2O$ or $R^6S(O)_2NH$ in which $R^6$ represents a $C_{1-6}$alkyl group optionally substituted by one or more fluoro, or $R^6$ represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^7)_3$ Si in which $R^7$ represents a $C_{1-6}$alkyl group which may be the same or different;
$R^{2a}$ represents chloro;
$R^{2b}$ represents chloro;

$R^3$ represents a $C_{1-3}$alkyl group;
$R^4$ represents a group $CONHNR^8R^9$ in which $NR^8R^9$ represents piperidino; and
$R^5$ represents H.

3. A compound of formula I as claimed in either claim 1 or claim 2 for use as a medicament.

4. A pharmaceutical formulation comprising a compound of formula I according either claim 1 or claim 2 and a pharmaceutically acceptable adjuvant, diluent or carrier.

6. Use of a compound of formula I according to either claim 1 or claim 2 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

7. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, neurological disorders, neurological disorders , Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound of formula I according to either claim 1 or claim 2 to a patient in need thereof.

8. A compound as defined in either claim 1 or claim 2 for use in the treatment of obesity.

## ABSTRACT

The present invention relates to compounds of formula I and processes for preparing such compounds, their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.